REMARKS

This Response, filed in reply to the Office Action dated October 17, 2007, is believed to be fully responsive to each point of objection and rejection raised therein. Accordingly, favorable reconsideration on the merits is respectfully requested.

Claims 5 and 6 are rejected. Claims 1-4 and 7-26 are canceled herein without prejudice or disclaimer. Claim 5 is amended to incorporate the limitations of withdrawn Claim 4, and to better clarify Applicants' elected invention. New Claims 27-46 are introduced, support for which can be found in Claims 7-26 as originally filed. No new matter is added by way of this amendment. Entry and consideration of this amendment are respectfully requested.

Election/Restriction

On page 2 of the Office Action, the Examiner asserts that the hybridoma species elected by Applicants, namely KM8761, is not recited in the specification. The Examiner requests that Applicants indicate the CDR sequences of the antibody produced by the KM8761 hybridoma.

In response, Applicants note that the CDR sequences elected in response to the restriction requirement mailed July 13, 2007, namely SEQ ID NOs: 5-7 and 8-10, are the CDRs of the antibody produced by the KM8761 hybridoma.

Further, for clarity in the record, Applicants respectfully point out that on page 2 of the Office Action, the Examiner acknowledges Applicants' election of "SEQ ID NOs: 8-9 for CDR's 1-3 of [the] light chain variable region." Applicants believe the Examiner intended to refer to SEQ ID NOs: 8-10, as these sequences were elected by Applicants in the reply to the restriction requirement submitted August 27, 2007.

Priority

Applicants thank the Examiner for acknowledging Applicants' claim for foreign priority and receipt of certified copies of the foreign priority documents, namely Japanese Application Nos. 2003-406590 and 2004-155141.

Objections to Claims 5 and 6

On page 3 of the Office Action, the Examiner objects to Claims 5 and 6 for the following reasons.

1. The Examiner asserts that Claims 5 and 6 depend from non-elected claims which have been withdrawn from further consideration. The Examiner asserts that Applicants are required to amend the instant claims to recite the limitations of the non-elected dependent claim(s).

Solely to advance prosecution, Applicants herewith amend Claim 5 to include the subject matter of withdrawn Claim 4. Applicants respectfully submit that the amendment overcomes this aspect of the objection.

2. The Examiner objects to recitation of the abbreviated terms "TARC" and "MDC," as recited in Claim 8. The Examiner asserts that such abbreviations should be spelled out the first time they appear in the claims.

Applicants note that Claim 8 is canceled, rendering the objection moot.

Withdrawal of the objections are therefore respectfully requested.

Claims 5 and 6 are Enabled Under 35 U.S.C. § 112

On page 4 of the Office Action, the Examiner rejects Claims 5 and 6 under 35 U.S.C. § 112, first paragraph, for allegedly lacking enablement.

1. In the first aspect of the rejection, the Examiner asserts that Claims 5 and 6 encompass an anti-human CCR4 antibody containing only three CDRs found in either the heavy chain, or the light chain.

The Examiner contends that the specification fails to provide sufficient guidance to allow the skilled artisan to make and use the various amino acid sequences recited in the instant claims. Specifically, the Examiner asserts that one of skill in the art would be unable to predict which additional CDRs could be paired together to form a functional anti-human CCR4 antibody.

The Examiner further contends that it is "well-established" that the formation of an intact antigen-binding site generally requires the association of complete heavy and light chain variable regions of a given antibody, inasmuch as the amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity of the antibody. The Examiner asserts that "it is expected that all of the heavy and light chain CDRs [must be present] in their proper order and in the context of framework sequences which maintain their required conformation [to produce an antibody] having functional antigen binding sites." In this regard, the Examiner contends that "even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function."

In setting forth the rejection, the Examiner cites to Rudikoff *et al.* (*PNAS*, 1982, 79:1979-1983) to assert that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function.

Further, the Examiner cites to Rader *et al.* (*PNAS*, 1998, 95:8910-8915) to assert that the pairing of either the heavy or light chains of a rodent antibody with the corresponding chain selected from a human polypeptide library is unpredictable, and that certain antibodies cannot be humanized using this approach.

For the above reasons, the Examiner asserts that "it is unlikely that the [claimed] antibodies [containing] only three CDRs in either [the] heavy or light chain would [specifically bind to] an extracellular region of human CCR4," and that undue experimentation would be required to make and use the claimed antibody commensurate in scope with that claimed.

Applicants respectfully disagree, and traverse this aspect of the rejection in view of the following remarks.

First, Applicants respectfully submit that the Examiner improperly relies on Rudikoff *et al.* to broadly assert that the state of the art of antibody production is unpredictable. Specifically, Applicants note that Rudikoff *et al.* disclose that S107 subclones (i.e., antigen-binding variants of S107) are vastly antigen reactive, since only "0.1-1%" of the clones do not precipitate in soft agar assays. Page 1980, Results and Discussion, first sentence. Furthermore, at page 1982 of Rudikoff *et al.*, the researchers state the opposite of what the Examiner concludes: "We have characterized another primary variant of S107 that has decreased antigen binding and a single amino acid substitution in the fifth residue of its J segment (39). However, it is clear that all substitutions need not and probably do not affect antigen binding. For example, the heavy chain from the P-Cho-binding myeloma protein M167 (35) differs from that of S107 at 13 positions (8 in hypervariable regions including a size difference) and yet has an association constant for hapten only slightly lower than S107. We have previously shown that, among anti-1,6-galactan-binding myeloma proteins, as many as eight or nine substitutions may occur in hypervariable

regions with no significant effect on hapten affinity or specificity (13)." (Emphasis added.) Applicants assert that one skilled in the art would readily understand that the result relied upon by the Examiner in Rudikoff *et al.* is an anomaly, and not representative of the state of the art, nor even representative of the results obtained by Rudikoff *et al.* Despite the Examiner's contention that the predictability of CDR mutagenesis is low, Rudikoff *et al.* actually disclose the contrary, that hypervariable regions are highly tolerant of mutagenesis with regard to retaining antigen-binding characteristics.

Contrary to the Examiner's position, the art is rife with the use of scFv (single-chain Fragment variable) antibodies. For example, Aires da Silva *et al.* (attached herewith), at page 527, disclose the production of functional rabbit anti-Vif VH single-domain antibodies. Further, Tanaka *et al.* disclose the use of intracellular antibody capture using scFc phage antibody libraries, to isolate single-domain VH "intrabodies," which have been demonstrated to possess greater affinity for antigen than the parental antibody containing heavy and light chains. Page 1110, column 2, lines 44-48. Further, Tanaka *et al.* (attached herewith) conclude that "binding of the anti-RAS scFv33 to antigen can occur through the VH domain alone." Page 1110, column 2, last sentence. Further still, on page 1115, column 2, first full paragraph, Tanaka *et al.* disclose that isolated VH domains are "ideal for binding specifically and with high affinity to antigen *in vivo*" and that "VL alone should possess the same property." Thus, despite the Examiner's assertion that it is "well-established that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions of a given antibody," the state of the art at the time of filing clearly discloses the routine production of single chain antibodies with binding affinities comparable, or better, than antibodies with heavy and light chains.

Applicants respectfully disagree with the Examiner that undue experimentation would be required to practice the invention as claimed, and assert that the Examiner's application of the law is inconsistent with the Court's findings in *In re Wands*[1], wherein it was held that "a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." (Emphasis added.) Consistent with the holding in *In re Wands*, a requirement even for extensive screening does not preclude a finding of enablement. In view of the skill level and technical knowledge possessed by one of skill in the art of antibody mutagenesis, the detailed guidance provided by the examples in the specification regarding the testing of antibodies for CCR4-binding activity, and the art-recognized techniques for antibody screening to isolate antibodies having a desired activity, Applicants submit that the experimentation required to perform the claimed invention would not be undue, but merely routine.

Withdrawal of this aspect of the rejection is therefore respectfully requested.

2. In the second aspect of the rejection, the Examiner asserts that the specification fails to provide sufficient *in vivo* or *in vitro* evidence demonstrating that a composition

[1] Extensive screening to isolate a claimed cell was not undue when the required methods are routine in biotechnology. *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). Further, the fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983), aff'd. sub nom., *Massachusetts Institute of Technology v. A.B. Fortia*, 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985). See also *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404. The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. *In re Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976). M.P.E.P. § 2164.01.

comprising the claimed anti-CCR4 antibody and G-CSF is able to treat all the tumors encompassed by Claim 5. Further, with regard to Claim 6, the Examiner asserts that the specification is not enabling for the treatment of all hematopoietic organ tumors, which encompasses leukemias, Hodgkin's lymphoma or non-Hodgkin's lymphoma.

The Examiner, however, acknowledges that the specification is enabling for the treatment of murine tumor cells expressing human CCR4, *in vitro*, and for reducing the burden of grafted tumors in mice when administered with G-CSF, *in vivo*.

To support a finding of lack of enablement, the Examiner contends that pharmaceutical therapies in the absence of *in vivo* clinical data are unpredictable because (1) the protein may be inactivated before producing an effect (i.e., by proteolytic degradation, immunological inactivation, or short half-life), (2) the protein may not reach the target area, and (3) "other functional properties, known or unknown," may make the protein unsuitable for *in vivo* therapeutic use, i.e., such as adverse side effects prohibitive to the use of such treatment.

The Examiner further asserts that in the absence of predictive data between *in vitro* inhibition, and *in vivo* efficacy in humans, one of skill in the art would be unable to predict the efficacy of the antibody in counteracting the cause or manifestation of Hodgkin's disease or leukemia.

To support her reasoning, the Examiner asserts that "experimental protocols usually are conducted under defined conditions wherein the antagonist and the stimulus/insult occur at the same or nearly the same time [and that] immunomodulation is much easier to achieve under such controlled conditions than that experienced in the human disorders or diseases such as Hodgkin's disease and leukemia targeted by the claimed invention."

Applicants respectfully disagree, and traverse the rejection in view of the following remarks.

Initially, Applicants note that the claims as amended recite "CCR4-expressing tumors."

Regarding the Examiner's asserted reasons for the unpredictability of pharmaceutical therapies *in vivo*, Applicants refer the Examiner to the myriad of therapeutic antibodies for the treatment of hematological malignancies known in the art (which have been shown to be efficacious *in vitro* and *in vivo*, and are FDA-approved), such as Retuximab®, Tositumomab® and Ibritumomab® (for the treatment of non-Hodgkin's lymphoma), which bind CD20 on B-lymphocytes, Alemtuzumab® (for the treatment of B-cell chronic lymphocytic leukemia (B-CLL)), which binds to CD52 on mature lymphocytes, and Mylotarg® (for the treatment of acute myeloid leukemia (AML)).

In view of the above, the Examiner's position that antibody therapy *in vivo* is unpredictable because such antibodies may be inactivated prior to producing an effect, or that the antibody may not reach the target area, clearly lacks factual support because other antibody therapies currently in use for hematological malignancies are efficacious. Indeed, the Examiner's arguments in this regard appear to pertain to therapeutic antibodies as a whole, despite the fact that the art describes a plethora of therapeutic antibodies that are efficacious in treating malignancies *in vivo*.

With regard to the Examiner's assertion that in the absence of predictive data between *in vitro* inhibition, and *in vivo* efficacy in humans, one of skill in the art would be unable to predict the efficacy of the antibody exemplified in the specification, Applicants respectfully disagree.

First, Applicants note that in the instant specification, and as acknowledged by the Examiner, the claimed anti-CCR4 antibody is tested for cytotoxicity both *in vitro* and *in vivo*.

Specifically, Example 1, the results of which are shown in Figure 1, demonstrates the enhanced cytotoxicity of the claimed anti-CCR4 antibody in combination with the cytokines IL-2 or IL-15. Further, Example 6 demonstrates that the administration of the claimed antibody in combination with G-CSF, *in vivo*, has a greater effect in reducing tumor burden than administration of either treatment alone. Thus, Applicants clearly demonstrate through *in vivo* experimentation that the claimed combination is effective in reducing the burden of CCR4-expressing tumor cells. In this regard, Applicants point out that the grafting of tumor cells into mice as an *in vivo* model for the analysis of tumor development or regression is well-known, and well-accepted in the art. The Examiner is respectfully reminded that, pursuant to MPEP §2164.02, "the examiner must also give reasons for a conclusion of lack of correlation for an *in vitro* or *in vivo* animal model example. A rigorous or an invariable exact correlation is not required, as stated in *Cross v. Iizuka*, 753 F.2d 1040, 1050, 224 USPQ 739, 747 (Fed. Cir. 1985)." (Emphasis added.)

Further still, Applicants disclose in at least paragraphs [0003]-[0005] of the published specification that CCR4 is overexpressed in leukemia and lymphoma cells, such as ALK-positive anaplastic large cell lymphoma, adult T-cell leukemia, and chronic T-cell leukemia. One of ordinary skill in the art would readily understand that by virtue of such overexpression, such cells represent a preferential target for cytotoxic anti-CCR4 antibody.

Thus, in view of the above, Applicants respectfully submit that one of skill in the art would understand that the use of therapeutic antibodies for the treatment of hematological malignancies is routine in the art, and that considering Applicants' *in vivo* data, and the art-recognized expression of CCR4 on T-cell leukemia and lymphoma cells, the use of cytotoxic anti-CCR4 antibodies would be useful for the treatment of CCR4-expressing tumors.

Accordingly, withdrawal of this aspect of the rejection is respectfully requested.

3. In the third aspect of the rejection, the Examiner asserts that the KM2760 antibody is required to practice the claimed invention, and consequently, it must either be known and readily available to the public or obtainable by a repeatable method set forth in the specification, or the cell line or hybridoma which produces this antibody should be deposited. The Examiner acknowledges Applicants' deposit of hybridoma clone KM2160 on August 12, 2004, with the International Patent Organism Depository, National Institute of Advanced Industrial Science and Technology, AIST Tsukuba Central 6, 1-1, Higashi 1-chome Tsukuba-shi, Ibaraki, Japan (Accession Number FERM BP-10090). However, the Examiner asserts that Applicants are required to satisfy that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent in U.S. patent applications., and that providing such assurances would obviate the rejection.

Applicants note that elected SEQ ID NOs: 16 and 18, as shown in the specification, disclose the heavy and light chain variable regions, respectively, of a humanized antibody that may be used to practice the claimed invention. From the disclosure of these amino acid sequences, and the knowledge possessed by the skilled artisan, it would be mere routine experimentation for one of skill in the art to reproduce an antibody having these heavy and light chains, and thus possess the requisite antigen-binding specificity. Accordingly, Applicants respectfully submit that a deposit is not required to practice the invention as claimed. Similarly, SEQ ID NOs: 11 and 12, as shown in the specification, disclose the heavy and light chain variable regions, respectively, of a human chimeric antibody that may also be used to practice the claimed invention.

Accordingly, withdrawal of this aspect of the rejection is respectfully submitted.

Claims 5 and 6 are Patentable Under 35 U.S.C. § 102

On page 9 of the Office Action, Claims 5-6 are rejected under 35 U.S.C. § 102(b) as being anticipated by Shitara *et al.* (U.S. Patent Application Publication No. 2003/0175273).

The Examiner alleges that Shitara *et al.* disclose a method comprising administering a medicament comprising a combination of a recombinant anti-CCR4 antibody and a pharmaceutically active agent, wherein the agent is G-CSF, citing paragraphs [0159]-[0163] and [0229]-[0251]. The Examiner asserts that the antibody of Shitara *et al.* appears to be the same or nearly the same as that of the instant application. The Examiner further alleges that Shitara *et al.* disclose that the antibody is a human chimeric antibody, or a human CDR-grafted antibody.

Applicants respectfully disagree, and traverse the rejection in view of the following remarks.

Applicants note that the portion of Shitara *et al.* relied upon by the Examiner only contemplates the conjugation of a radioisotope, protein or agent to an antibody. Shitara *et al.* neither teach nor reasonably suggest administering the antibody and agent as independent components, as is Applicants' claimed invention. Accordingly, Shitara *et al.* fails to teach each and every element of the claimed invention, as is required to maintain a rejection under section 102.

Withdrawal of the rejection is therefore respectfully requested.

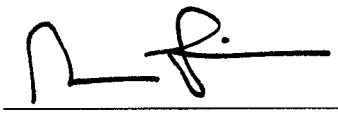
Conclusion

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the

Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,



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